Epitomes

Important Advances in Clinical Medicine

Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association, and the summaries were prepared under its direction.

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Fungal Sinusitis in Immunocompetent Patients

SINUSITIS is a common problem in otherwise healthy persons, especially those with atopic disease. The most common etiologic agents are bacteria and viruses. Less commonly, sinusitis may be caused by a variety of fungi. Fungal sinusitis in an immunocompromised patient is often a fulminant life-threatening disease and is most commonly caused by *Aspergillus* species or the agents of mucormycosis (zygomycosis). In an immunocompetent patient, fungal sinusitis is usually chronic and is diagnosed when surgical treatment is carried out in patients who have not responded to antimicrobial therapy for presumed bacterial sinusitis. Therefore, the possibility of fungal sinusitis should be considered in patients with sinusitis unresponsive to appropriate antibacterial therapy.

Three categories of fungal sinusitis have been described: invasive, chronic noninvasive, and allergic. Invasive disease is characterized by local extension with necrosis of soft tissue and bone and most commonly occurs in immunocompromised patients. Noninvasive sinusitis is typified by the presence of a "fungus ball" in one or more of the paranasal sinuses. A local inflammatory response without tissue destruction results. *Aspergillus* species are the most common causes of noninvasive fungal sinusitis. The diagnosis and treatment of this condition are primarily surgical; antifungal therapy probably has no role. Allergic sinusitis is also caused primarily by *Aspergillus* and is found in patients with asthma and recurrent sinusitis. Histologic examination of the sinuses reveals mucus containing fungal hyphae as well as eosinophils and Charcot-Leyden crystals. Whether this disorder is distinct from noninvasive sinusitis is not completely established.

More recently, the dematiacious (pigmented) fungi have also been associated with sinusitis. These include *Bipolaris* (formerly called *Drechslera* or *Helminthosporium*), *Exserohilum, Curvularia,* and *Alternaria.* Patients frequently have atopic disease, such as hay fever and nasal polyposis, but are otherwise healthy. The most common symptoms are chronic nasal discharge or obstruction that has not responded to antibacterial agents or nasal corticosteroids. Sinus radiographs and computed tomography show sinus opacification without an air-fluid level. A computed tomographic scan sometimes shows local bony destruction. Fungal hyphae are found in the mucus from surgical specimens and, less commonly, bone invasion, necrosis, or both are found. Thus, this disorder overlaps all three classes of fungal sinusitis mentioned earlier. Although primarily a noninvasive disease, there may be local invasion, and patients frequently give a history of allergic symptoms. The prognosis is variable. In a few patients, cerebral extension develops despite surgical and antifungal therapy. Some have required several surgical procedures to stabilize their disease, but others have apparently been successfully treated with a single surgical procedure.

Until more is known about the natural history of sinusitis caused by the pigmented molds, these patients should probably be treated with antifungal therapy in addition to surgical debridement. Amphotericin B is the most effective agent currently available, and ketoconazole has some in vitro activity. Itraconazole, an investigational triazole, shows good in vitro activity against these fungi and may prove to be a satisfactory oral agent for treating patients with chronic fungal sinusitis.

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REFERENCES

Adam RD, Paquin ML, Petersen EA, et al: Phaeohyphomycosis caused by the fungal genera *Bipolaris* and *Exserohilum*—A report of 9 cases and review of the literature. Medicine (Baltimore) 1986; 65:203-217

Katzenstein AA, Sale SR, Greenberger PA: Allergic *Aspergillus* sinusitis: A newly recognized form of sinusitis. J Allergy Clin Immunol 1983; 72:89-93

McGuirt FW, Harrill JA: Paranasal sinus aspergillosis. Laryngoscope 1979; 18:1563-1568

Washburn RG, Kennedy DW, Begley MG, et al: Chronic fungal sinusitis in apparently normal hosts. Medicine (Baltimore) 1988; 67:231-247

Continuous Estrogen-Progestin Therapy in Postmenopausal Women

ESTROGEN REPLACEMENT THERAPY in postmenopausal women has been widely advocated for the relief of climacteric complaints and the prevention of osteoporosis. In addition, the use of standard doses of conjugated estrogen (0.625 mg) has been shown to increase high-density-lipoprotein (HDL) cholesterol levels by about 15% and is associated with a relative risk for cardiovascular disease of 0.2 to 0.7 com-

pared with that of nonusers. At present, contraindications for postmenopausal estrogen replacement are personal history of breast cancer, endometrial cancer, or deep venous thrombosis. An adverse effect of estrogen therapy is endometrial hyperstimulation, which can lead to hyperplasia and eventually carcinoma. The relative risk estimates for endometrial cancer associated with estrogen replacement range from 2 to 12, depending on the duration of estrogen use and the cumulative dose. The incidence of endometrial hyperplasia in patients receiving continued unopposed estrogen therapy is 15% to 50%, but this can be reduced to zero if progesterone is added for at least ten days each month. The duration of the progestin treatment each month is more important than the dose in preventing endometrial hyperplasia. The progestational side effects appear to be more dose-dependent and include symptoms like abdominal bloating, headache, depression, and acne. Another serious effect is a reduction in the beneficial effect of estrogen on the HDL cholesterol.

A standard regimen for hormone replacement therapy has been the cyclic administration of estrogen and progestin. A new approach has recently been introduced involving the use of continuous combined treatment. Four studies have looked at the daily use of estrogen—conjugated equine estrogen, 0.625 mg, or estradiol valerate, 2 mg—and a low-dose progestin, such as medroxyprogesterone acetate, 2.5 to 5 mg, or norethindrone, 0.35 to 2 mg, in 148 postmenopausal women observed for 3 to 18 months. These treatments were consistently shown to produce amenorrhea with an inactive endometrium, while alleviating climacteric symptoms. The amount of breakthrough bleeding tended to decrease with the increasing doses of progestin used. Most of the bleeding occurred during the first four months of treatment, and by the ninth month spotting was uncommon regardless of the dose used. It is reassuring that despite breakthrough bleeding, no endometrial hyperplasia was found during continuous treatment in any of the women studied. Two short-term trials using daily conjugated equine estrogen, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg, showed either no change in lipoprotein levels or a statistically significant decrease in total and low-density-lipoprotein cholesterol levels from pretreatment values.

The optimal formulation for daily hormonal therapy in postmenopausal women is still unknown. It seems reasonable to initiate treatment with one of the combinations already studied, like conjugated estrogen plus low-dose medroxyprogesterone acetate. After several months the progestin dose may be adjusted, either downward to the lowest dose that maintains amenorrhea, or upward if breakthrough bleeding occurs. If bleeding persists on a higher dose, it would be prudent to do a gynecologic evaluation and possible endometrial biopsy. If breakthrough bleeding is minimal after a few months of treatment, standard guidelines for routine pelvic examinations and Pap smears could be followed. If larger studies continue to show a complete suppression of endometrial proliferation on continuous combined therapy, there should be no need to do regular endometrial biopsies on these patients. There are many other issues to be considered in the management of perimenopausal women who still have cyclic bleeding, but these will not be discussed here.

In summary, the use of a daily combination of estrogen with a very-low-dose progestin may be an easy, convenient, and safe way to provide hormone replacement in postmenopausal women. This treatment seems preferable to conventional therapy because it avoids cyclic bleeding and reduces progestational side effects while protecting the endometrium. It may also prevent the climacteric symptoms that some women experience during the period of estrogen withdrawal. Larger long-term studies are still needed to document that the benefits of adding continuous low-dose progestin to estrogen replacement outweigh the risks.

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REFERENCES

Ernster VL, Bush TL, Huggins GR, et al: Benefits and risks of menopausal estrogen and/or progestin hormone use. Prev Med 1988; 17:201-223

Prough SG, Aksel S, Wiebe RH, et al: Continuous estrogen/progestin therapy in menopause. Am J Obstet Gynecol 1987; 157:1449-1453

Sporrong T, Hellgren M, Samsioe G, et al: Comparison of four continuously administered progestogen plus oestradiol combinations for climacteric complaints. Br J Obstet Gynaecol 1988; 95:1042-1048

Ganciclovir for Cytomegalovirus Retinitis

RETINITIS IS the most common manifestation of cytomegalovirus (CMV) disease in immunocompromised patients, especially those with the acquired immunodeficiency syndrome (AIDS). Although CMV infection can cause disease at other sites, such as the esophagus, colon, and central nervous system, the retina is the most commonly involved site in patients with AIDS. Although CMV infection is an unusual index AIDS diagnosis, this infection will develop in 5% to 10% of patients at some time during the course of the disease. Lengthened survival due to improved antiretroviral chemotherapy and the suppression of *Pneumocystis carinii* pneumonitis will doubtless increase the incidence of other opportunistic infections such as CMV.

Ganciclovir has recently been approved by the Food and Drug Administration for the treatment of life-threatening CMV retinitis. It is a nucleoside analogue like acyclovir. Clinical trials with ganciclovir began in 1984, and clinicians (especially those caring for AIDS patients) quickly came to the conclusion—in the absence of prospective, comparative studies—that the drug was effective. It was not until several years later, however, that a series of prospective and retrospective clinical trials provided convincing evidence of efficacy.

Ganciclovir is currently recommended for the treatment of sight-threatening CMV retinitis. Patients with this disease have visual symptoms, and retinoscopy shows the typical changes of CMV retinitis—perivascular hemorrhages and whitish "exudates" (actually, necrotic retinal tissue). Asymptomatic patients with rapidly progressive retinitis moving toward the macula may also warrant treatment. Therapy for patients with asymptomatic, nonprogressive or slowly progressive peripheral CMV retinitis or those with end-stage (blinding) retinitis in one eye is still controversial. It is not yet clear that the benefits of long-term ganciclovir therapy exceed the risks of toxicity in such patients.

Treatment with ganciclovir is traditionally divided into two phases: the initial treatment phase—usually called the "induction" phase, by analogy with cancer chemotherapy—and the later phase of long-term chemosuppression, usually called the "maintenance" phase. The drug is always given intravenously. The induction dose is 5 mg per kg of body weight given every 12 hours for 14 days; the dose needs to be reduced for patients with renal insufficiency. All patients receiving induction should be placed on a maintenance